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EXAMINER	
BRUNOVSKIS, P	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/392,822	Applicant(s) YU ET AL.	
	Examiner Peter Brunovskis	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The request filed on 9/04/01for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/392,822 is acceptable and a CPA has been established. Claims 1-31 are pending in the instant application. A review of the filed Transmittal sheet does not provide evidence of new amendments to the claims; consequently, the Rejections previously set forth in the Office Action of 3/02/01 remain for the reasons set forth therein. For Applicants' convenience the contents of the 3/02/01 Office Action is reproduced in the Action on the CPA as follows.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 10 and 22 are rejected under 35 U.S.C. 101 because the disclosed invention is inoperative and therefore lacks utility. Claims 10 and 22 recite adenovirus vectors comprising an alleged cell status-specific TRE comprising a HRE comprising SEQ ID NO:1. However, careful inspection of the sequence of SEQ ID NO:1 reveals no HRE, nor any sequence (or reverse complement sequence) matching the rat enolase-1 promoter, asserted to carry a HRE which is critical to the operation of the claimed vectors. The sequence listed in Fig. 2 as SEQ ID NO:1

appears instead to resemble a depiction of a 3'-5' sequence (i.e. reverse sequence) from the rat enolase promoter entered in the SEQUENCE LISTING in a 5'-3' direction. Neither this sequence (i.e. SEQ ID NO:1) nor its reverse complement would be predicted to share any structural properties responsive to hypoxic induction. The specification does not provide any well established utility for such vectors, nor do such vectors meet the limitations recited in the rejected claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 8, 9, 11, 13, 18, 21, and 26-31 (and dependent claims) are indefinite in their recitation of the term "cell-status specific transcriptional regulatory element (TRE)" since the specification does not clearly define the phrase or its metes and bounds. The specification provides a circular definition of the term: "the term 'cell status-specific TRE' is one that allows a cell status-specific TRE to function" (p. 12, lines 11-13) and attempts to qualify the definition by stating that the term applies to "a cell which exhibits a particular physiological condition,

including, but not limited to, an aberrant physiological state" (lines 13-14) and a condition wherein "cell status...refers to a given, or particular, physiological state (or condition) of a cell, which is reversible and/or progressive...generated internally or externally" (lines 15-17). It is not clear what, if anything, is excluded from the definition as set forth thereof.

Applicants arguments filed 12/06/00 have been fully considered but they are not persuasive, since amending the claim from "TRE comprising a cell status-specific TRE" to "TRE is a cell status-specific TRE" does not clarify what are the metes and bounds of the cell status-specific TRE.

Claims 9 and 21 (and dependent claims) are indefinite in their recitation of the term "hypoxia responsive element" or "HRE" since it is unclear how this term is defined or what its metes and bounds are. Apart from a HRE comprising SEQ ID NO:1, it is unclear what other elements are embraced by this term. For example, given a promoter-enhancer region responsive to hypoxic conditions, it is unclear which specific element(s) thereof can be considered to be excluded from the definition of "hypoxia responsive" (i.e. specific enhancer binding sequence, TATA box etc.).

Claims 10 and 11 (and dependent claims) are indefinite in their recitation of the term "cell-cycle specific element"since it is unclear how this term is defined or what its metes and bounds are. Further, it is not clear how claim 12 further limits claim 11 since it is unclear what is actually the cell cycle specific element from the E2F-1 gene that claim 12 is directed to.

Claim 13 is indefinite in its recitation of the term "heat-inducible element" since it is unclear how this term is defined or what its metes and bounds are. Apart from heat inducible elements comprised of heat shock promoters, it is unclear what other elements or promoters are embraced by this term.

Claim 14 (and dependent claims) is indefinite in its recitation of the term "cell type-specific TRE" since the definition in the specification (i.e. p. 18, lines 13-21) does not clearly define its metes and bounds. For example, the definition begins with a vague and relative definition describing an element that is "preferentially functional in a specific type of cell relative to other types of cells" (lines 13-14). Part of the vagueness is that gene expression is responsive to exogenous signals in a particular cell context; however, the claims do not provide any context or conditions for comparison. The description goes on to suggest that a "cell type-specific" TRE can be active in more than one cell type--an apparent misnomer. In attempting to explain the metes and bounds of embodiments embraced by this broader interpretation, the description provide a circular definition without sufficient clarity for one of skill in the art to determine its metes and bounds:

> "when a cell type-specific TRE is active in more than one cell type, its activity is restricted to a limited number of cell types, i.e. it is not active in all cell types" (lines 18-20).

Thus, it is not clear what is what metes and bounds apply to the term "cell type-specific TRE".

Claim 16 recites the limitation "the prostate cell-specific TRE" in line 1. There is insufficient antecedent basis for this limitation in the claim. Base claim 15 recites a cell type-

specific TRE that is prostate cell specific. It is not clear what part of the cell type-specific TRE of claim 15 that is prostate cell specific is a prostate cell-specific TRE.

Claim 18 (and dependent claims) is indefinite in its recitation of the phrase "adenovirus gene under the transcriptional control of a TRE" since it is unclear what structural relationship exists between this TRE the cell status-specific TRE or the cell-type specific TRE

Claim 25 is indefinite because it is unclear what cell context applies to the claimed subject matter, i.e. is the composition drawn to an isolated cell or does it embrace, e.g. a host cell in an organism?

Claims 26-28 are indefinite because there is no clear structural nexus between the recited adenovirus vectors of (or according to) claim 1 and the phrase "allow[ing] a cell status-specific TRE to function". For example, it is not clear whether the introduction of the adenovirus vectors allow a cell status-specific TRE to function in a cell or whether such an introduction allows a cell status-specific TRE *in the vector* to function in a cell. In addition, the claims are indefinite because it is unclear whether they are drawn to methods in isolated or cultured cells, or whether they broadly embrace *in vivo* methods of propagation and/or gene delivery in an organism.

Claim 26 is indefinite in its recitation of the phrase "adenovirus specific for cells which allow a cell status-specific TRE to function" since it is not clear what is meant by the word "specific" in the context of the cell; further, the claim is incomplete because it is unclear what structural relationship- or requirements exist between the "cells" and the "adenovirus according to

claim 1, or what context applies to said cells that would "allow [i.e. not prevent] a cell status-specific TRE to function" either with respect to the adenoviral vector or the cell.

Claim 27 is an incomplete claim since the method steps do not clearly relate back to the preamble which recites "[a] method of conferring selective cytotoxicity on a target cell". For example, the method recites the step of "contacting a cell" though it is not clear with what--with the adenovirus or some other unspecified composition that allows a cell status-specific TRE to function with an adenovirus. Further it is unclear what structural relationship- or requirements exist between the "target cells", the cell status-specific TRE, and the "adenovirus vector of claim 1". Moreover, it is not clear what is meant by the term "selective" within the context of a "selective cytotoxicity on a target cell" that is implicitly "selected for contact".

Claim 28 is indefinite and incomplete since it is unclear what structural relationship- or requirements exist between the "adenovirus according to claim 1", the "tumor cell", or the cell status-specific TRE. Additionally the claim is indefinite because the method steps do not clearly relate back to the preamble, which recites a method of suppressing tumor growth, whereas one of the method steps recites introducing the adenovirus vector of claim 1 into a tumor cell. It is not clear how introduction of a vector in a cell (singular) allows suppression of tumor growth, since tumors are composed of many cells. Further, the response, filed 12/06/00 states that "[n]either claim 27 nor claim 28 recite a method for gene delivery, that is, delivery of a heterologous gene into a cell for its expression to achieve a therapeutic purposes, which is the standard definition of gene therapy" (p. 5, top paragraph). However, such an assertion appears inconsistent with claim

28 which recites "[a] method for suppressing tumor growth...wherein introduction of the adenovirus results in suppression of tumor growth". The specification provides no evidence of any well-established non-therapeutic utility directed to a method for suppressing tumor growth.

Claim 29 is indefinite in its recitation of "cell status specific promoter" as distinguished from a "cell status specific enhancer" since the term "promoter" used in the context of claims 29-31 appears to relate to a minimal promoter. Because the specific nature of the cell status specific element is unclear, it is not clear whether either one of the cell status specific promoter or the cell status specific enhancer can alone constitute a functional cell status-specific regulatory element". The recited context of claims 29-31 suggest that the promoter of claims 29 and 31 is a minimal promoter. However, if this is the case, it appears unlikely that such an element can be considered by itself, a functional cell status regulatory element in accordance with the definition on p. 12.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to method or compositions comprising cell status-specific TREs and/or cell type-specific TREs. Additional claims recite embodiments wherein the cell status-specific TRE and/or the cell type-specific TRE comprises an additional element (e.g. HRE, element from E2F-1 gene, heat-inducible element, etc.) or wherein the cell status specific TRE comprises a cell status specific promoter or cell status specific enhancer. In none of the claims is it actually clear how to distinguish or determine what constitutes the metes and bounds of the terms cell status-specific TRE, cell type-specific TRE, cell status specific promoter or cell status specific enhancer. The definitions are vague or circular in nature and do not provide an adequate written description for one of skill in the art with a given molecule of DNA to determine whether that molecule possesses regulatory elements in accordance with the recited terms.

The "status" of cells is determined by the overall conditions or stimuli for growth that they are receiving. One of the problems with the term "cell status-specific TRE" or "cell type specific TRE" is that neither of these proposed genus groups possesses a recognizable core structure identifying members of this genus. Moreover, it is not clear what is included or excluded from these terms inasmuch as they depend from a vague notion of an ever changing cell status *context* in which a regulatory element may or may not meet the vague definition set forth. Gene regulation is extremely complex. A promoter that is responsive to stress conditions, such as heat, low O_2 or radiation is in fact responsive to a complex array of signal transduction events culminating in activation of an assortment of multiprotein complexes, comprising many standard, garden variety of transcription factors, such as AP-1, NF-κB, and CREB, or even basal

transcription factors such as TBP etc. Each of these factors has specificity for particular short stretches of sequence. Would the recognition elements for any one of the multiple factors involved in the activating, for example, the "hypoxia-inducible" egr-1 promoter be considered a cell status-specific element? Additionally, would a DNA sequence recognized by a transcription factor responsive to hypoxia (see e.g. p. S129 left col., Dachs et al., Br. J. Cancer, 74(Suppl. XXVII):S126-S132, 1996) meet the limitations of a cell status-specific TRE? Claim 11 broadly recites a TRE comprised of a cell cycle specific element. Claim 12 attempts to further limit the claim by reciting the TRE comprises a cell cycle-specific element from the E2F-1 gene. However, it is not clear what part of the E2F-1 gene, or indeed what part of any of the claimed subject matter, actually constitutes a cell status-specific TRE.

An adequate written description of a DNA or regulatory element therefrom requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA or regulatory element itself. It is not sufficient to define an element solely by its principal biological property, i.e. element that allows a cell status-specific TRE to function, *or by what it is not*, i.e. distinct from "cell type", which relates to a differentiation state, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNAs carrying that specific regulatory element. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a

nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all DNAs that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived.

Applicants attention is drawn to the decision of *The Regents of the University of California v. Eli Lilly and Company* (CAFC, July 1997) wherein it was stated:

> In claims involving chemical materials, generic formulas usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate written description of the claimed genus. In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what it achieves as a result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. *See In re Wilder*, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

Because Applicants have failed to provide an adequate written description of the materials used in the compositions and methods claimed and because there is no evidence that Applicants possessed any TRE embodiments beyond those disclosed and/or known in the prior art, the rejected claims fail to meet the written description requirement under 35 U.S.C. 112, first paragraph.

Claims 1-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining enablement are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation....Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Factors that can be used in evaluating undue experimentation include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

The subject invention pertains to methods and compositions comprising a replication-competent adenovirus comprising an adenovirus gene essential for replication under transcriptional control of a cell status-specific transcriptional regulatory element (TRE) and/or a cell-type specific TRE. Because the specification fails to provide a clear picture the describing the genus groups comprised of cell status-specific TREs and/or a cell-type specific TREs and because the specification fails to provide adequate guidance on how to *make* the broad range of adenovirus embodiments commensurate with the claimed subject matter, it does not provide an enabling disclosure. First, one cannot make (or teach how to make) something that has not been adequately described. Secondly, the claimed invention cannot be enabled unless the disclosure provides sufficient guidance teaching one of skill in the art how to identify and determine when he has actually made an embodiment that meets the functional limitations in the claim. The claims are broadly drawn to a virtually unlimited range of cells each differently susceptible to cell status specific stimuli that differentially affect gene expression. The specification does not provide sufficient guidance concerning, for example, assays for evaluating or determining whether threshold levels of response have been obtained that are commensurate with identifying a cell status specific element. Further, even if such guidance were provided, it would require undue experimentation to determine all the members of such a genus and then determine how to use these newly identified TREs in the context of an adenoviral vector in accordance with the teachings in the specification.

Additionally, the specification broadly embraces a variety of different essential (e.g. claim 1) or non-essential (e.g. claim 18) adenovirus genes under the control of a cell status-specific TRE. First, the specification does not enable the use of replication competent adenoviruses comprising non-essential adenoviruses regulated by cell-status specific TREs, since the disclosure is predicated on the use of replication competent vectors whose *replication* is conditionally regulated in a cell status-specific manner. Thus, the specification fails to provide specific guidance on how to use the claimed invention comprising cell status-specific TRE-regulated *non-essential* adenoviral genes, since these embodiments would not be predicted to show any particularly useful phenotype relative to a wildtype adenovirus. Additionally, the specification contemplates the use of major late genes (i.e. claim 4) as further limiting essential adenovirus genes for operable linkage to the cell status-specific TRE but states elsewhere that "all of these [i.e. late] genes (typically coding for structural proteins) are *probably* required for adenoviral replication" (emphasis added; p. 31, lines 19-21). However, the specification fails to teach which genes actually meet the "essential for viral replication" limitation recited in base claim 2; thus the specification fails to teach which late genes to use in accordance with claim 2. Furthermore, the specification does not provide an enabling disclosure commensurate with the scope of replication-competent adenoviruses comprising wildtype E1A transcription units, capable of promoting replication in normal adenoviral target cells through the native E1A promoter, independent of the nature of the operable linkage to the late genes. Specifically, the specification fails to provide sufficient guidance or a reasonable expectation of predictability or success in using e.g.

adenoviruses carrying a wildtype E1A transcription unit and a secondary replication gene operably linked to a cell status-specific TRE. These viruses replication-competent with respect to adenoviral DNA, independent of the cell status-specific TREs and it is unclear whether abrogating the natural coordinate regulation through introduction of TRE-redirected expression of other essential products would lead to a sufficient level of viral particle production in vivo, so as to enable their use in cells.

Additionally the specification fails to provide sufficient guidance teaching how to make and use replication-competent adenoviruses comprising *additional* cell status-specific TRE and/or cell-type specific TRE-directed transcription units with a sufficiently predictable expectation of success. First, the specification provides little guidance concerning specific TRE combinations to use in the claimed methods. Even with embodiments carrying just one exogenous TRE, the specification fails to provide sufficient evidence for predictable, cell status-specific replication (and/or cell-type-specific transgene expression when using more than one TRE). In this case, the specification fails to provide evidence of having overcome previously reported problems of unpredictability observed when using heterologous cellular promoters in a replication-competent adenovirus. For example, using a *replicative* adenovirus vector, Babiss et al. (J. Mol. Biol., 193:643-650, 1987) have previously shown that liver cell-specific promoters exhibit reduced specificity compared to their normal activities in a cellular context; although cell-specific expression from certain promoters was not significantly changed in certain cell types when placed in a replicating adenoviral background, delivery to other non-liver cells (i.e. HeLa) resulted in

high levels of transgene expression, independent of the "tissue-specific" promoter chosen (see e.g. abstract). These results are consistent with the more recent findings of Shi et al. which suggest that negative elements are present in the adenoviral genome that appear to negatively impact on the specificity of heterologous tissue-specific promoters inserted into adenoviral vectors (Shi et al., Hum. Gene Ther., 8:403-410, 3/1/97). In the absence of further guidance and/or working examples related to choice of cells and promoters that do *not* reduce promoter specificity when inserted in an adenoviral vector such that repication specificity is also not lost, the practice of using the claimed embodiments in accordance with the recited limitations (i.e. status- and/or cell-type-specific replication or transgene expression) is highly unpredictable. Failure to maintain specificity of expression would likely ensure that replication is not limited in accordance with the predicted experimental design as set forth by the TREs recited in the instant claims.

Further, the specification fails to provide sufficient guidance commensurate with the scope of the claimed subject matter as it relates to replication-competent adenoviruses carrying any and all TREs and/or transgenes. Bett et al. have previously shown that adenovirus vectors have a packaging capacity for exogenous DNA that cannot exceed 105% of the wildtype virus genome (J. Virol., 67(10):5911-5921, 10/93). Thus, a replication-competent wildtype virus can only accommodate a net gain of about 1.8 kb of nucleic acid sequences. However, the claimed subject matter broadly embraces embodiments comprising e.g. 2.2 kb of TRE sequences in claim 22, not to mention heterologous transgenes as disclosed in e.g. pp. 31-33. The specification does not teach how to make recombinant adenoviruses exceeding the packaging capacity for particle

production, nor does the specification provide sufficient guidance or evidence of a well established utility for using replication-competent, packaging-deficient adenoviruses.

Claims 25-28 broadly embrace compositions or methods directed to cells comprising the adenovirus vectors of the claimed invention. To the extent that the claims are directed to in vivo methods (i.e. claims 26-28) or cell compositions in a multicellular organism (claim 25), the specification does not provide an enabling disclosure commensurate with the breadth of the claimed subject matter. First, the specification provides no evidence for any well-established *non-therapeutic utility* for such methods or compositions *in an in vivo context*. With regard to the non-enabled compositions and methods as they are drawn to therapeutic gene delivery, it is noted that at the time filing, successful use of gene therapy was not routinely obtainable by those skilled in the art. W. French Anderson, one skilled in the art, recently concluded: "[e]xcept for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human diseases [Nature, vol. 392:(Supp.), 1998, p. 25, first paragraph]...[s]everal major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered. The reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basic understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types, how *in vivo* immune defenses can be overcome, and how to manufacture efficiently the vectors that we do make" (p. 30, next to last paragraph). Concurring with Anderson, Verma and Somia state that "[t]he Achilles heel of gene therapy is gene delivery...and

[t]hus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (Nature, vol. 389, 1997, p. 239, col. 3, 2nd paragraph)...[a]lthough more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (p. 239, col. 1, 2nd paragraph). Although the instant application seeks to address some of the above-described limitations as they relate to poor delivery and/or targeting, it does so in the face of a high degree of unpredictability.

In fact, the physiological art is recognized in general as being unpredictable (MPEP 2164.03). As set forth *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In view of the failures associated with attempts to treat diseases by gene therapy as taught by Anderson and Verma, gene therapy should only be considered predictable in not being shown to work. Thus, in view of the particularly high degree of unpredictability and lack of success in the gene therapy art at the time of filing, gene therapy can only be considered predictable in being shown not to work. Thus to overcome these teachings in the art and enable the instantly claimed methods, the specification would need to supply direct, correlative guidance as to a specific

replication-competent adenovirus: i.e. description of cell status-specific and/or cell type-specific TREs and their operable linkage to adenoviral genes and/or transgenes, therapeutic expression levels (if applicable), routes of delivery, and dosage amounts/frequencies effective for alleviating symptoms of disease using the claimed replication-competent adenoviruses.

Despite being considered by some, the "gold-standard" for gene transfer, adenoviral vectors were recognized at the time of filing as not having yet been developed to overcome the problems described by Anderson and Verma. Curiel reviewed the state of the adenoviral vector art as it relates to gene therapy as follows:

> "To date, several groups have sought to exploit the fundamental advantages of adenovirus by using it in specific contexts where the recognized limitations were judged to be less important. For example, it was thought that the issue of the widespread tropism of the virus could be circumvented by administering the vector by direct injection, particularly in the context of tumors. However, in phase I human trials, dissemination beyond the injected site was found. Application to "compartmentalized" disease has also met with problems. For example, poor gene transfer efficiency has been noted following administration into the pleural space for therapy of mesothelioma, and in the peritoneum, effective use of antitumor gene therapy has been limited by concurrent gene transfer of the liver with subsequent toxicity. Further limitations have arisen in the application to pulmonary disease. Here, prior clinical experience had indicated that the virus had a natural tropism for the respiratory tract; therefore, direct administration of vector to the airways for cystic fibrosis therapy seemed a rational approach. In reality, the achieved levels of gene transfer were lower than expected, because differentiated airway epithelial cells lack sufficient adenoviral receptors and the integrins required for viral internalization. Therefore, even in these apparently favorable anatomic locations there is a strong case for developing a vector with cell-specific targeting properties" (p. 159, Ann. NY Acad. Sci., 886:158-171, 1999).

The claimed invention is drawn to the use of replication-competent adenoviruses carrying cell status-specific and/or cell type-specific promoters designed to restrict adenoviral replication

and/or transgene expression only to particular subsets of cells or particular subsets of cells in a certain metabolic state. This is distinguished from cell targeting, since the claimed adenoviral vectors are no different with respect to ubiquitously targeting and infecting a broad range of cells carrying the coxsackie-adenovirus receptor (CAR). Most, if not all, of the claimed cell status specific or cell type specific transcriptional regulatory elements (TRE) are either from tumor-specific promoters; normal, cell-cycle-regulated promoters active in all cell types at one time or another; naturally inducible in the microenvironment of tumor cells (e.g. hypoxic conditions); or inducible in conjunction with treatments routinely used in cancer patients (e.g. radiation, heat). Thus, most, if not all of the TREs disclosed in the instant application are directly or indirectly related to conditions associated with cancer or abnormal proliferation or treatment conditions employed in methods for treating cancer. The specification does not provide sufficient specific guidance or basis for using the claimed invention for any therapeutic treatment, *in particular non-cancerous diseases*. In particular, the specification fails to provide a single in vivo working example. Further, the specification fails to provide specific guidance for any specific combination of cell status-specific TREs operably linked to an adenoviral gene that is enabled for use in treating a given disease. Basically, the specification lacks the appropriate specific guidance referred to above that would be necessary to overcome the problems and the unpredictability in the art. Specifically, there are no teachings in the specification that would provide the artisan with any treatment regime to achieve a therapeutic benefit by in gene therapy and provides no correlation between adenoviral compositions, routes of delivery (e.g. intratumoral, intravenous

etc.), dosage amounts/frequencies, and specific diseases or tumors treatable by using the adenovirus compositions of the instant application.

Since the teachings in the specification largely describe the use of replication-competent adenovirus for use in killing cells, such as tumor cells, it should be noted that with respect to in vivo delivery to tumors, there is essentially no guidance concerning the specific routes of adenoviral vector administration for a given tumor, nor any specific guidance concerning delivery across the blood-organ or blood-brain barriers. At the time of filing Jain reviewed the multiple barriers limiting delivery of therapeutics to solid tumors and teaches that "tumors often develop in ways that hinder each of these [delivery] steps" (J. Contr. Rel., 53:49-67, 4/1998; see e.g. abstract, p. 49). Moreover, Hobbs taught that different tumors exhibit varying degrees of vascular permeability reflected in pore cutoff sizes for therapeutic agent uptake depending on the tumor. In certain subcutaneous microenvironments, for example, these cutoff sizes were found to drop under certain conditions to less than 7 nm, significantly smaller than the size of adenoviral particles (Hobbs et al., Proc. Natl. Acad. Sci. USA, 95:4607-4612, 4/98; see e.g. p. 4607, right column). The specification does not address problems of delivery to solid tumors, nor does it provide a sufficient expectation of a therapeutic benefit using the claimed compositions commensurate with the claimed subject matter.

In conclusion, the specification does not address the problems discussed above and it does not provide adequate guidance teaching one of ordinary skill in the art how to make and use adenoviral compositions in accordance with the in vivo methods embraced by the rejected claims.

The instant invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). The compositions and methods of the claimed invention constitute such a "germ of an idea".

Applicant's arguments filed 12/06/00 have been fully considered to the extent they apply to the present grounds for lack of enablement, but they are not persuasive. First, clarification is sought concerning the scope of instant claims 27 and 28. The response seems to waffle on the question of whether the claims are drawn to in vivo gene delivery or therapy, since the response contends that "[n]either claim 27 nor claim 28 recite a method for gene delivery, that is, delivery of a heterologous gene into a cell for its expression to achieve a therapeutic purposes, which is the standard definition of gene therapy" (p. 5, top paragraph). However, as noted above, such an assertion appears inconsistent with claim 28 which recites "[a] method for suppressing tumor growth...wherein introduction of the adenovirus results in suppression of tumor growth". Moreover, Applicants appear to argue the question of whether the claimed invention is enabled for gene therapy. For example, Applicants assert that "no correlation to achieving therapeutic expression of genes is required because the claims do not recite delivery of therapeutic genes to

target cells" and further contend that "'tailoring' or optimizing a method for a specific disease would not require undue experimentation for the skilled artisan" (p. 6). First, the point about recitation of therapeutic genes is not well taken, since the cytolytic replication-competent adenoviruses of the claimed invention are at least conceptually therapeutic in view of their design which is predicted to promote at least a certain degree of tumor-specific cell killing. Regardless of whether the claims are or not drawn to in vivo therapy, the fact of the matter is that Applicants have failed to provide evidence of any well-established *non-therapeutic utility* for the subject matter of the rejected claims. Moreover, it should be noted that Applicants appear to have mischaracterized the evidence of record in claiming that "the specification will reveal that cell targeting is achieved by virtue of the TRE employed...provid[ing] for targeting of the adenovirus vector to the cell in the sense that adenovirus preferentially replicates in those cells....and allows for targeting to a desired cell that allows the TRE to function" (paragraph abridging pp. 5-6). To the contrary, the evidence of record does not support the notion that the adenovirus vectors of the claimed invention allow targeting to specific cell types, but rather preferential replication in those cells that have been infected and that are in a particular *cell status-specific state*. There is no discrimination of cells with respect to cell targeting. This point is important to note, given the teachings of Curiel concerning the limitations of adenoviral vectors at the time the invention was made, specifically, their inability, upon systemic administration, to home in on and selectively infect and replicate in diseased cells to the exclusion of the large background of non-diseased coxsackie-adenovirus receptor-positive cells.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Note: With respect to the claimed subject matter embracing in vivo therapeutic treatment, the following rejection applies to the extent that the claims read on methods involving e.g. use of gene therapy vectors for *developing* therapeutic protocols to *test* various possible treatments for gene therapy in experimental animals. The prior art rejection is not to be construed as an indication that the claimed or anticipated methods are *enabled* for therapeutic use.

Claims 1-9, 11-21, and 23-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Henderson et al. (WO 97/01358, 1/16/97) in view of Hallenbeck et al. (WO 96/17053, 6/6/96), Walther et al. (Mol. Biotechnol., 6:267-286, 1996), Dachs et al. (Nat. Med., 3(5):515-520, 5/97), Dachs et al. (Oncol. Res., 9:313-325, 12/1/1997), Advani et al. (Semin. Oncol., 24(6):633-638, 12/97), and Parr et al. (Nat. Med., 3(10):1145-1149, 10/97).

Henderson et al. disclose conditionally replicative-competent adenoviruses designed to limit cytolytic replication to specific cell types due to operable linkage of a cell type-specific TRE to adenoviral genes essential for replication, and optionally carrying a heterologous gene product (e.g. abstract and p. 52, claim 21). Henderson discloses a preferred embodiment comprising

replication competent adenovirus comprising a prostate specific antigen (PSA) TRE comprising a cell status specific enhancer (nucleotides from 503 to 2086 of SEQ ID NO:3) and a cell status specific promoter (nucleotides from about 5285 to about 5836 of SEQ ID NO:3) operably linked to the adenovirus E1A promoter (i.e. CN706, p. 33-38; as evidenced by p. 49, lines 16-19 of the specification). Henderson does not explicitly teach any of the cell status-specific TREs as disclosed in e.g. claims 9-13.

Hallenbeck et al. discloses conditional replication competent adenoviruses to limit cytolytic replication to specific cell types due to operable linking an adenoviral early gene to any one of a number of different tissue or tumor-specific promoters (see e.g. abstract and claims 1 and 3). Hallenbeck further teaches that the adenovirus vectors of the claimed invention can further comprise a heterologous gene product, such as one that is toxic for cells in the targeted tissue for use in a method of killing cells (e.g. p. 23, lines 1-4 and claim 8). Hallenbeck does not explicitly teach any of the cell status-specific TREs as disclosed in e.g. claims 9-13.

Walther et al. reviews the state of the art concerning targeted vectors for gene therapy of cancer and discloses several types of cell status-specific TREs including those comprising a hypoxia responsive elements and heat-inducible elements (see e.g. "Tumor Therapy-Inducible Gene Therapy" section p. 279-281). Walther teaches a class of radiation-inducible and heat-inducible promoters comprising cell status-specific TREs which "serve as a source for suitable promoters to be exploited for expression regulation of therapeutic genes" (p. 279), since radiotherapy and hypothermia, two well-established therapies of human cancers, induce a broad

class of cell status-specific promoters that "provide a great potential for the construction of "therapy-inducible" vectors to express auxiliary therapeutic genes that might *act synergistically* with conventional therapies of human tumors" (emphasis added, p. 281). Walther does not explicitly recite the term "cell status-specific TRE" nor does Walther refer to hypoxia-inducible response (HRE) elements or cell cycle-specific elements.

Dachs et al. (Nature Med.) disclose an experimental approach for targeting tumors wherein the hypoxic environment of a tumor can be exploited for activating heterologous gene expression driven by a hypoxia-response element (HRE) comprising a cell status-specific TRE contained in the mouse PGK-1 promoter. Dachs teaches that use of HREs can be used to develop gene therapy against the drug- and radiation-resistant hypoxic population in tumors. Dachs does not explicitly disclose replication-competent adenovirus vectors comprising cell status-specific TREs.

Dachs et al. (Oncol. Res.) reviews the state of the art concerning targeted vectors for gene therapy of cancer and provides a detailed account essentially supporting the use of cell status-specific TREs:

> "Another level of specificity can be added to selective delivery by targeting gene expression. Transcriptional promoters that are specifically functional in single tissues, or are *active in specific disease states, or are induced by tumor-specific conditions* have been identified during basis research into cancer progression and can be utilized for targeted expression" p. 314; emphasis added).

More specifically, Dachs discloses several types of cell status-specific- and cell type-specific TREs including those comprising hypoxia responsive- and radiation-responsive TRE elements (see e.g.

"Condition-Targeted Expression" section, p. 318-319). Dachs teaches that "severe hypoxia is also a physiological condition specific to tumors, which makes it a potentially exploitable target...[such that they]...have utilized hypoxia response elements (HRE) derived from the oxygen-regulated phosphoglycerate kinase gene to control gene expression in human tumor cells in vitro and in experimental tumors" (abstract, p. 313) and that the abnormal hypoxic conditions characterizing almost all solid tumors is "a major hindrance to therapy", since "cells in this aberrant environment can remain viable and are often chemo- and radioresistant" (p. 318). Dachs further reviews several studies targeting transgene expression to tumorous or ischemic tissues, wherein transgene expression is selectively induced on account of their operable linkage to HRE elements responsive to the hypoxic environment of the diseased tissues. Additionally, Dachs describes the benefits of adenoviral delivery of a Egr-1-controlled TNF-α construct in conjunction with radiation which was shown to result in extensive intratumoral vascular thrombosis and necrosis, whereas no thrombosis was detected in treated normal tissue. Finally, Dachs teaches that:

> "choosing only one criteria for selectivity, such as targeting delivery to proliferating cells or tissue-specific expression, is not sufficient, as nonspecific toxicity has been reported. Only by *combining* the most successful strategies in cancer gene therapy approaches will a successful clinical treatment emerge" (emphasis added, p. 322).

Dachs does not teach the use of cell cycle-specific or heat-inducible TREs.

Advani et al. discloses the benefits of employing cell status-specific TREs comprised of radiation-inducible promoters and teaches that "[i]ncreasing local tumor control by combining

radiotherapy and gene therapy may improve the outcome of cancer treatments by decreasing tumor mass more effectively while limiting systemic toxicity. Advani does not teach the use of cell cycle-specific, heat-inducible-, or hypoxia-inducible TRE elements.

Parr et al. discloses adenoviral vectors comprising transgenes operably linked to a E2F-1 promoter containing a cell status-specific TRE that can mediate tumor-selective gene expression in vivo, allowing for eradication of established gliomas with significantly less normal tissue toxicity than seen with standard adenoviral vectors (abstract). Parr further point out that since many tumors contain mutations that affect the Rb/E2F pathway, and since de-repression of the E2F-1 promoter occurs in cancer cells in vivo, viral vectors incorporating E2F-responsive promoters can be exploited to design viral vectors that mediate tumor-selective gene expression" (abstract and p. 1147, right col.).

At the time the invention was made it would have been obvious to one of ordinary skill in the art to substitute or combine methods the cell type specific TREs in the conditionally replication-competent adenovirus vectors of Henderson or Hallenbeck with the cell status-specific TREs disclosed by Walther, Dachs, Advani, or Parr, since Walther, Dachs, and Advani teach the benefits of combining tumor specific, cell type specific, and/or cell status-specific regulatory elements, particularly since cell status specific regulatory elements are inducible by well-established cancer treatment, e.g. radiation and hypothermia, and because Walther, Dachs, and Parr teach that operably linking radiation-inducible, heat-inducible, hypoxia-inducible or cell cycle-inducible regulatory elements (comprising cell status-specific TREs) allows for more

effective and selective transgene expression and tumor eradication with significantly less normal tissue toxicity than seen with standard adenoviral vectors. Substituting and/or combining the cell type-specific regulatory elements of Hallenbeck and Gregory with the cell status-specific TREs of Walther, Dachs, Advani, or Parr would have been in accordance with the goals and teachings of Hallenbeck and Gregory, particularly since the resulting embodiments would have been predicted, with a high expectation of success, to augment the intratumoral virus inoculum, permit greater flexibility in the treatment of tumors, and/or produce a positive synergistic effect in conjunction with other well-established cancer treatments. Thus the invention was prima facie obvious at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 14-16, 18-22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 8, and 32 of copending

Application No. 09/151,376. Although the conflicting claims are not identical, they are not patentably distinct from each other because the rejected claims fully embrace claims 1-4, 8, and 32 of the copending application

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office action. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Brunovskis whose telephone number is (703) 305-2471. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Patent Analyst, Patsy Zimmerman whose telephone number is (703) 308-8338.

Deborah Crouch

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